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TITLE: Prevention of Breast Cancer and Therapy Resistance Using Novel Therapeutic Approaches

PRINCIPAL INVESTIGATOR: Rajeshwar Rao Tekmal, Ph.D.

CONTRACTING ORGANIZATION: University of Texas Health Science Center
San Antonio, TX 78229-3900

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Fort Detrick, Maryland 21702-5012

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1. REPORT DATE: July 2017	2. REPORT TYPE: Annual	3. DATES COVERED: 1 Jul 2016 - 30 Jun 2017

4. TITLE AND SUBTITLE:

Prevention of Breast Cancer and Therapy Resistance Using Novel Therapeutic Approaches

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5b. GRANT NUMBER:
W81XWH-16-1-0294

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S):
Principal Investigator
   Rajeshwar Rao Tekmal, Ph.D.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

**University of Texas Health Science
Center at San Antonio
San Antonio, Texas 78229-3900**

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research And
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

A number of recent studies including form our group have shown that exogenous ERβ expression or its induction/activation by ERβ agonists result in blocking the growth of ERα-positive breast cancer cells. The central hypothesis of this study is that ERβ activation and/or its overexpression shifts the balance from oncogenic functions of ERα to tumor-suppressing actions of ERβ, thus preventing initiation and progression of breast cancer. In addition, ERβ activation and/or its overexpression prevent and or delay the development of resistance and restores hormonal sensitivity resistant tumors. This study is focused on testing the therapeutic efficacy of ERβ agonists in preventing and as well as treating and blocking the progression of breast cancers. Significant findings during first year funding period are: a) Using transgenic animal model we have shown both LY500307 and S-Equol reduced mammary growth and initiation of malignant changes; b) this is the first study to investigate the role of ERβ in the context of breast cancer prevention; c) ERβ agonists were able to restore sensitivity to endocrine therapy resistant cells to hormonal therapy; and d) we have identified novel signaling molecules associated with ERβ agonists mediated protection.

15. SUBJECT TERMS
Endocrine therapy resistant breast cancers; breast cancer prevention; estrogen receptor beta agonists, therapeutic efficacy of estrogen receptor beta agonists

16. SECURITY CLASSIFICATION OF: U			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON: USAMRMC
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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

A number of recent studies including form our group have shown that exogenous ERβ expression or its induction/activation by ERβ agonists result in blocking the growth of ERα-positive breast cancer cells. Based on our findings, **we hypothesized** that ERβ activation and/or its overexpression shifts the balance from oncogenic functions of ERα to tumor-suppressing actions of ERβ, thus preventing initiation and progression of breast cancer. In addition, ERβ activation and/or its overexpression prevent and or delay the development of resistance and restores hormonal sensitivity of resistant tumors. This study is focused on testing the therapeutic efficacy of ERβ agonists in preventing and as well as treating and blocking the progression of breast cancers.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

Endocrine therapy resistant breast cancers; breast cancer prevention; estrogen receptor beta agonists, therapeutic efficacy of estrogen receptor beta agonists;

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.

<mark>There are no changes in project direction or in the scope of work</mark>

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

<mark>During the first year funding period we have studied the following major goals (tasks):</mark>
Major goal (task) 1: Determine efficacy of ERβ agonists to prevent breast cancer and to prevent or delay the development hormonal resistance.

Subtask 1 (1-24 months): Establish that ERβ agonists prevent the incidence of breast cancer in genetically engineered animal models.

Subtask 2 (1-24 months): Establish that ERβ agonists block progression and recurrence of breast cancer immune-competent tumor models?

Major goal (task) 2: Determine the efficacy of ERβ agonists to prevent or delay development of resistance in endocrine therapy naïve breast tumors.

Subtask 1 (1-12 months): Test whether ERβ agonists restore sensitivity to AE/AI endocrine therapy using various endocrine therapy sensitive and resistant cells.

Major goal (task) 3: Elucidate how ERβ signaling network influences the role of ERβ agonists in preventing and overcoming hormonal resistance

Sub goal (subtask 3-SW; 1-24 months): Establish the mechanisms of prevention/tumor suppressive functions of ERβ

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

1. **Major Activities:**
During the first year funding period we have initiated the work as stated in Statement of Work

- We have completed the approval of the IACUC protocol
- Obtained approval for collection of tissues from breast cancer patients from UTHSCSA tumor bank and institutional IRB under exemption category.
- Increased transgenic animal breeding for generating required transgenic mice.
- Initiated experimental work (Major tasks) as indicated in statement of work is shown below:
    1. Established the preventive role of ERβ agonists in the prevention of breast cancer using transgenic animal model

    2. Determined efficacy of ERβ agonists to restore sensitivity to endocrine therapy in resistant breast cancer cells

    3. Elucidated how ERβ signaling network influences the role of ERβ agonists in preventing breast cancer using transgenic models.

2. **Specific Objectives:**

Objective 1: Establish that ERβ agonists prevent the incidence of breast cancer in genetically engineered animal models (**Major Task 1-Subtask 1:1-24 months**).

Objective 2: Establish that ERβ agonists block progression and recurrence of breast cancer immune-component tumor models (**Major Task 1-Subtask 2: 1-24 months**).

Objective 3: Test whether ERβ agonists restore sensitivity to AE/AI endocrine therapy using various endocrine therapy sensitive and resistant cells (**Major Task 2-Subtask 1: 1-12 months**).

Objective 4: Establish the role of phoshotyrosine switch involved in the endocrine-sensitizing activity of ERβ (**Major Task 3 - Subtask 1: 1-12 months**).

Objective 5: Establish the mechanisms of prevention/tumor suppressive functions of ERβ (**Major Task 3 - Subtask 3:1-24 months**).

3. Significant Results (outcomes):

Results for objective 1: *Establish that ERβ agonists prevent the incidence of breast cancer in genetically engineered animal models.* To test the therapeutic efficacy of ERβ agonists to prevent the initiation of breast cancer, our initial studies focused on MMTV-HER2/neu model. We have used the pubertal animals (n=9/group) and treated with ERβ agonist (LY500307 and S-equol). Mammary growth (ductal elongation and ductal branching) was examined after 4 months of continuous treatment. As shown in Figure 1, mammary ductal branching and hyperplasia in ductus and mammary labulo-alveolar structures were significantly affected with treatment when compared with control. There was no significant difference in the ductal elongation and also there was no change in the body weight (data not shown).
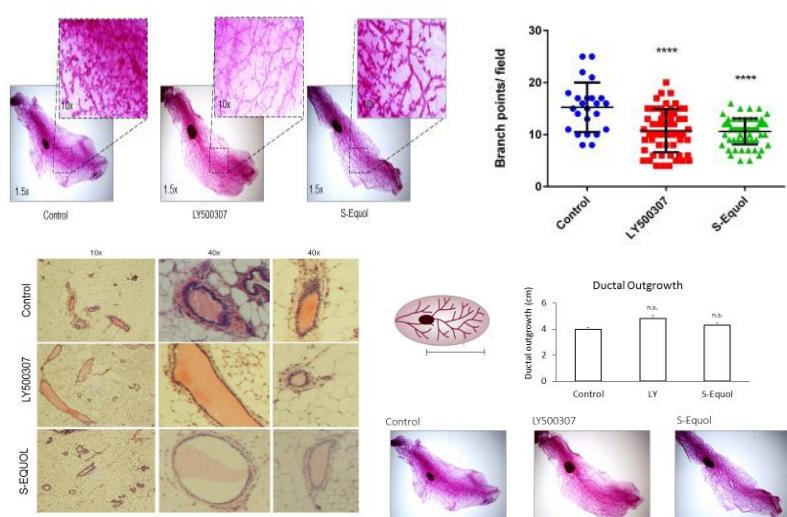

Figure 1. *Effect of ERβ agonists on the mammary growth/ prevention of pre/neoplastic changes (initiation of tumorigenesis): While there is no significant difference on the ductal elongation (lower left) with treatment with ERβ agonists, there was a significant reduction on mammary growth (labulo-alveolar/branching) (p<0.001) (upper right and left) compared to controls. There was also decrease or lack of devolvement hyperplasia in treated animals (lower left).*

Studies described here show that treatment with ERβ agonists affects mammary growth. Specifically significant decrease in the ductal hyperplasia and lateral ductal branching (labulo-alveolar growth) an indication of mammary growth and initiation of neoplastic changes clearly suggest ERβ agonists are very effective in preventing breast cancer initiation in experimental models studied. Studies that examines effect of these compounds on prevention and the tumor incidence with other models is in progress (ongoing study).

Results for objective 2: *Establish that ERβ agonists block progression and recurrence of breast cancer immune-component tumor models.* To test the therapeutic efficacy of ERβ agonists to block the tumor progression using immune-component breast cancer tumor models. We have used the D2A1 (BALB/c) and MM51 (FVB) murine model cells and tested their growth in the presence and absence of ERβ agonists employing cell growth and colony formation assays. In addition, we have tested effect of LY on tumor growth using both D2A1 and MM5I syngeneic mice tumor models. As shown in Figure 2, ERβ agonists (LY500307 and S-equol) were effective in blocking the both cell growth and colony formation. In addition, LY was very effective in reducing tumor growth in syngeneic mice compared to control. When combined with aromatase inhibitor (letrozole) the tumor growth was further reduced significantly. Ongoing will focus on testing effect of these compounds on the tumor progression (metastasis)
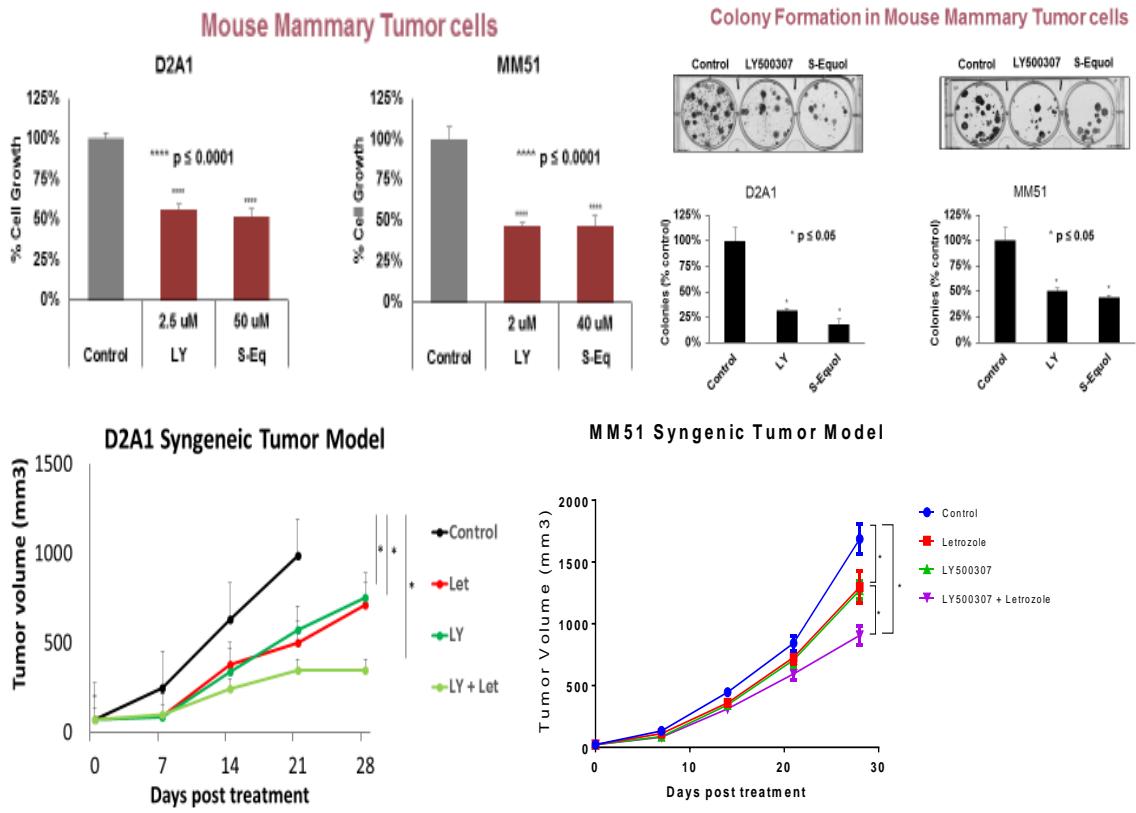
Figure 2. *Effect of ERβ agonists on in vitro and in vivo growth. LY500307 and S-Equol were effective in blocking the growth in culture (top left panels) and colony formation (top right panels). LY500307 was very effective in block tumor growth (p<0.001) in both syngeneic tumor models (bottom panels).*

Results for objective 3: Test whether ERβ agonists restore sensitivity to AE/AI endocrine therapy using various endocrine therapy sensitive and resistant cells.

To test the ability of ERβ agonists to affect the growth of both endocrine therapy sensitive and resistant breast cancers, we tested their growth using cell growth and colony formation assays.

As shown in figure 3, ERβ agonists (LY500307 and S-Equol) significantly affected the growth hormone sensitive breast cancer cells. We also tested the effect of these compounds using MCF7-LTLT an aromatase inhibitor (letrozole) resistant breast cancer cell line and a tamoxifen resistant breast cancer cell line (MCF7-TAM).

Data presented in figure 4 shows that both ERβ agonists affected the growth of aromatase inhibitor resistant breast cancer cells. Like, S-equol, LY500307 was very effective in blocking the growth of tamoxifen resistant breast cancer cells in culture, but its effect on anchorage independent growth (colony formation) was not significant. These observations suggest the unlike in letrozole resistant breast cancer cells the mechanism of action of these agents in tamoxifen resistant cells appears to be different. More studies are planned to help to learn the mode of action of these compounds in hormone therapy sensitive versus resistant tumors.
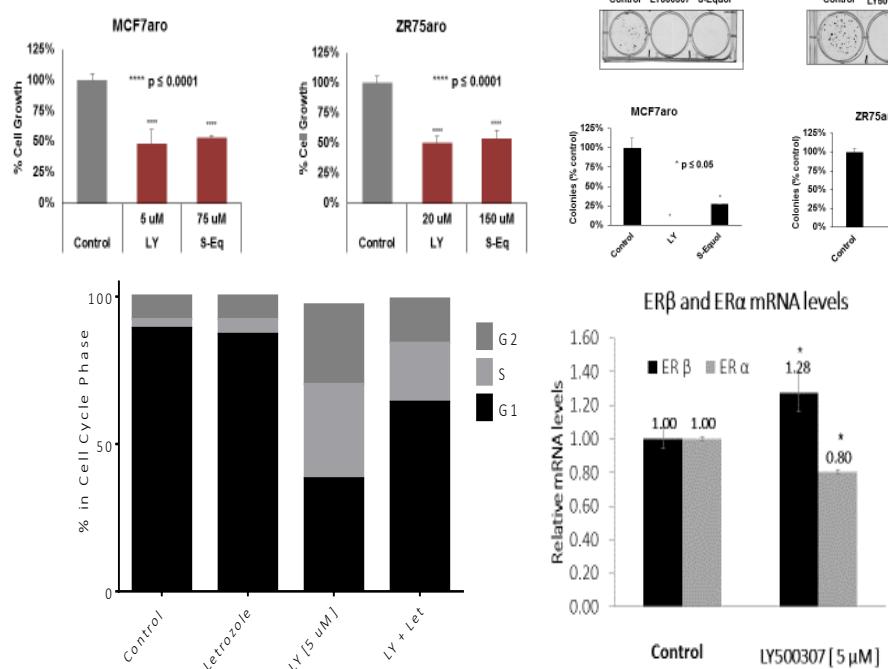
Figure 3. *Effect of ERβ agonists on the growth of hormone responsive breast cancer cells. LY500307 and S-Equol were effective in blocking the growth in culture (top left panel) and colony formation (top right panel). Unlike with letrozole, LY500307 appears to restrict the growth by affecting S and G1 phase of cell cycle (bottom left panel) and also affected the levels of ERα contributing change in the ratio of ERα/ERβ (bottom right panel).*
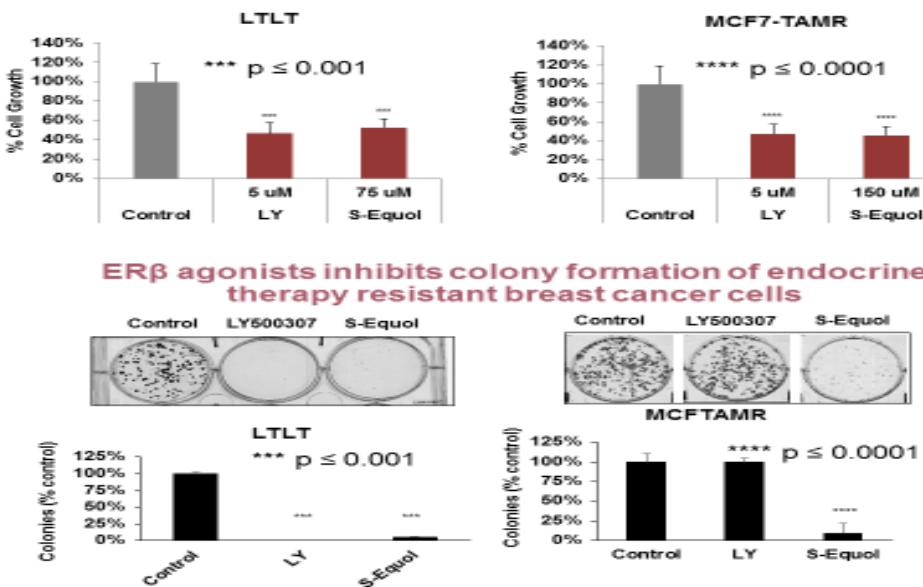

Figure 4. *Effect of ERβ agonists on the growth of hormone therapy resistant breast cancer cells. LY500307 and S-Equol were effective in blocking the growth of letrozole resistant breast cancer cells (top and bottom left panels). Both LY500307 and S-equol were effective in blocking the growth tamoxifen resistant cells (top right panel) but LY500307 not very effective in blocking colony formation (bottom right panel).*

Results for objective 4: _Establish the role of phoshotyrosine switch involved in the endocrine-sensitizing activity of ERß._

This work is in progress, it took more time than originally anticipated in generating stable clones with ERβ knock-in clones.

Results for objective 5: *Establish the mechanisms of prevention/tumor suppressive functions of ERβ*

 To examine the molecular mechanisms that are involved in the prevention of initiation of neoplastic changes in response to ERβ agonists, we used mammary tissues from studies described (Major goal 1, sub task 1) and analyzed using microarray analysis. Using computational analysis, we have determined changes in the expression of various genes whose expression either significantly increased or decreased during ERβ agonists-mediated prevention in transgenic animals.

As shown in figure 5, treatment with ERβ agonist resulted significant changes in the expression of various genes. While both ERβ agonists affected change in the expression of various genes and distinct set genes are modulated by these compounds. As shown in figure 5 we have also identified pathways that are effected ERβ agonists.
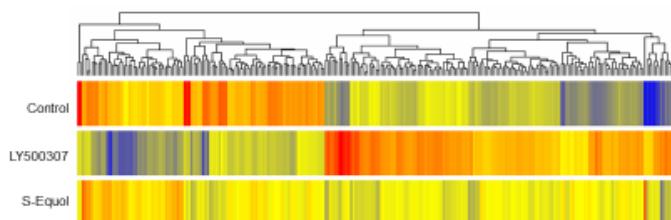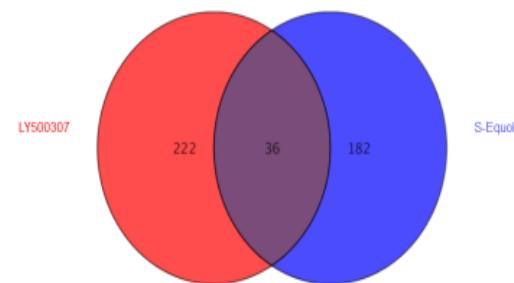

Figure 5: *Change in the expression of various genes involved in ERβ agonists-mediated prevention of neoplastic changes in transgenic mice.*

To further validate these observations, we have examined top few genes whose expression is significantly affected (either increased or decreased) using qRT-PCR analysis. Data presented in figure 6 confirms the observations seen with microarray analysis. These observations will be further expanded using tissues from tumor reduction and other studies as planned to learn the mechanism of action of ERβ agonists in preventing and blocking tumor progression.
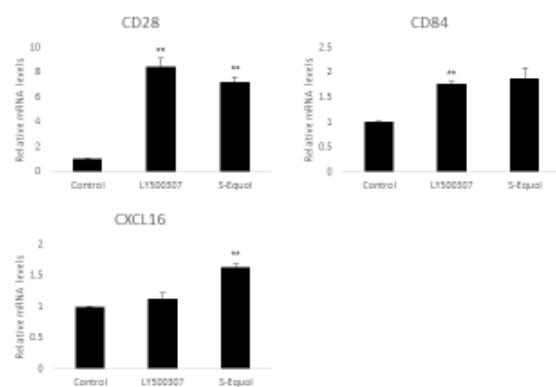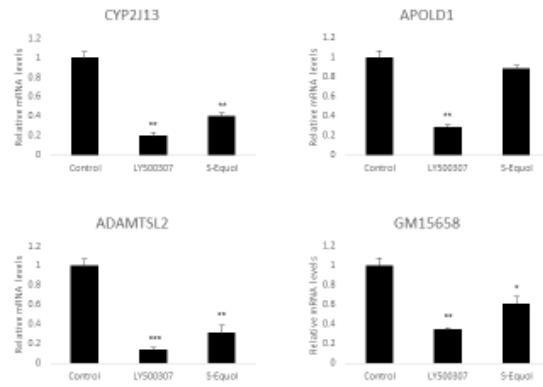

Figure 6: Validation of change in the expression of genes *involved in ERβ agonists-mediated prevention of neoplastic changes in transgenic mice.*

Major Findings/Conclusions:

- Using transgenic animal model we have shown that both LY500307 and S-Equol reduced mammary growth and initiation of malignant changes.
- First study to investigate the role of ERβ in the context of breast cancer prevention.
- ERβ agonists were able to restore sensitivity to endocrine therapy resistant cells to hormonal therapy.
- We have identified novel signaling molecules pathways associated with ERβ agonists mediated protection.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

During the first year, this project provided training opportunities for 5 students (1 graduate and 4 high school) and one post-doctoral fellow. All the students/fellows were trained in conducting oncology research using BC model cells, preclinical animal models, designing/analyzing research experiments and interpreting the data. In addition, Post-doctoral fellow was given an opportunity to train students, this provided an opportunity to sharpen his mentoring skills. Postdoctoral fellow was provided an opportunity to serve as mentor of rotating and high school students. Every week, PI spend an hour of assigned time mentoring about their research project, interpreting their results and discussing their career development plans. All students participated in weekly project meetings and presented their research progress. In addition, students/fellows were provided several professional development opportunities including participation in journal clubs, participation in UTH cancer center workshops, and attendance of grand rounds, and attendance of ethics seminar series. Further, postdoctoral fellow attended 2016 AACR SABCS and 2017 AACR annual meeting to present our research findings.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Initial findings were presented to scientific community at 2016 San Antonio Breast Cancer Symposium (international meeting attended by ~7500 from over 80 countries) and 2017 American Association of Cancer Research (AACR)

What do you plan to do during the next reporting period to accomplish the goals?

If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We are planning to present our findings at both national and international meeting at least once a year. We also are in the process of preparing manuscript to be published in a peer reviewed scientific journal

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

These studies provided evidence for therapeutic efficacy of estrogen receptor-β agonists in the prevention of breast cancer and to restore the sensitivity to endocrine therapy resistant breast tumors to hormone therapy in preclinical models. Once completed these studies will form a basis for clinical trial since the compounds tested are being explored for clinical use for other indications.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

The results of this study provided a rationale to examine the efficacy of ERβ agonists blocking the growth of ovarian and endometrial cancers. Gynecological Oncology fellow and Ob-gyn residents are engaged in these studies at our institute.

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:
- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state "Nothing to Report."
Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:
- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to Report

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes.

Remember that significant changes in objectives and scope require prior approval of the agency.

No changes and there is nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

It took more time to develop ERβ knock in cell clones to test the phosphotyrosine switch involved in the endocrine-sensitizing activity of ERβ. We have now made needed cell clones and the work is in progress (Major goal 3; subtask 1).

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

No changes to report

Significant changes in use or care of vertebrate animals

No changes to report

Significant changes in use of biohazards and/or select agents

No changes to report

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

No manuscripts were submitted in the first year as some experiments are still ongoing. We are planning to do that in the second year with concluded aspects this study.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

> None

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

> Samayoa, C., Krishnegowda, N.K, Vadlamudi, R.K., and Tekmal R.R.: Pre-clinical investigation of estrogen receptor β agonists for the treatment of breast cancer. 39th Annual San Antonio Breast Cancer Symposium, P6-11-15, 2016. Cancer Res 2017;77(4 Suppl):Abstract nr p6-11-15
>
> Ramasamy, K., Samayoa, C., Krishnegowda, N.K., Vadlamudi, R.K., and Tekmal R.R.: Potential therapeutic use of Estrogen Receptor β agonist in the prevention and progression of breast cancer using HER-2/neu mouse model. Proc. Am. Assn. Cancer Res., 108th Annual Meeting, Abstract 3616, 2017. Cancer Res 2017;77(13 Suppl):Abstract nr3616.doi:101158/1538-745-AM2017-3016

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

> None

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

> None

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

> None

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
    - *data or databases;*
    - *physical collections;*
    - *audio or video products;*
    - *software;*
    - *models;*
    - *educational aids or curricula;*
    - *instruments or equipment;*
    - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
    - *clinical interventions;*
    - *new business creation; and*
    - *other.*

None

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name:	**Rajeshwar Rao Tekmal, Ph.D**.
Project Role:	**Principal Investigator**
Researcher Identifier (e.g. ORCID ID):	UTHSCSA Faculty, Department of Ob-Gyn
Nearest person month worked:	3.6 months (30% paid effort on this project)
Contribution to Project:	Dr. Tekmal was involved in planning and execution of all research aspects and as well scientific and financial management of this grant
Funding Support:	Partially funded by USAMRC grant (BCRP151884; this grant) and UTHSCSA funds.

Name:	**Ratna K. Vadlamudi, Ph.D.**
Project Role:	**Co-Investigator**
Researcher Identifier (e.g. ORCID ID):	UTHSCSA Faculty, Department of Ob-Gyn
Nearest person month worked:	0.48 months (4% paid effort on this project)
Contribution to Project:	Dr. Vadlamudi was involved in planning and analysis of biomarker studies that examined molecular pathways
Funding Support:	Partially funded by USAMRC grant (BCRP151884; this grant), other grants and UTHSCSA funds.

Name:	**Rong Li, Ph.D.**
Project Role:	**Co-Investigator**
Researcher Identifier (e.g. ORCID ID):	UTHSCSA Faculty, Dept. of Molecular Medicine
Nearest person month worked:	0.36 months (3% paid effort on this project)
Contribution to Project:	Dr. Li was involved in planning and analysis of ERβ phsprorylation using ERβ knock in and knock out models
Funding Support:	Partially funded by USAMRC grant (BCRP151884; this grant), other grants and UTHSCSA funds.

Name:	**Kumaraguruparan Ramasamy, Ph.D.**
Project Role:	**Postdoctoral Fellow**
Researcher Identifier (e.g. ORCID ID):	UTHSCSA Staff, Department of Ob-Gyn
Nearest person month worked:	9 (Joined full-time effective October 1, 2016)
Contribution to Project:	Dr. Ramasamy has performed all molecular and cell culture work and assisted with animal studies
Funding Support:	USAMRC funded grant (BCRP151884; this grant)

Name:	**Naveen Krishnegowda, M.B.B.S.***
Project Role:	**Research Associate**
Researcher Identifier (e.g. ORCID ID):	UTHSCSA Staff, Department of Ob-Gyn
Nearest person month worked:	11 months
Contribution to Project:	Dr. Krishnegowda was responsible for maintenance and generation of all required animals from animal models and carried out animal work.
Funding Support:	UTHSCSA –Ob-Gyn Departmental and other support.

*This person being replaced with new research associate who will be supported by this grant beginning effective August 2017.

As there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."
If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

No change

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."
Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with

the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)
- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

<div style="border:1px solid">

Nothing to report

</div>

8. **SPECIAL REPORTING REQUIREMENTS**

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. **APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

See the attached copy of the abstracts presented at national and international meetings.

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Cancer Research

Poster Session Abstracts

Abstract P6-11-15: Pre-clinical investigation of estrogen receptor β agonists for the treatment of breast cancer

C Samayoa, NK Krishnegowda, RK Vadlamudi, and RR Tekmal

| Article | Info & Metrics |

Abstracts: 2016 San Antonio Breast Cancer Symposium; December 6-10, 2016; San Antonio, Texas

Abstract

Breast Cancer is the primary cause of cancer-associated mortality worldwide, and in United States alone, more than 250,000 women are diagnosed every year. Current breast cancer treatment strategies focus on Estrogen Receptor α signaling, given that the majority of cases diagnosed are ERα positive. These treatment strategies include endocrine therapies; such as anti-estrogens or aromatase inhibitors. Although, endocrine therapy has been demonstrated to be successful and effective, therapy resistance commonly arises and results in relapse. While current endocrine therapies focus on ERα signaling, emerging studies highlight the importance of Estrogen Receptor β. Unlike ERα, ERβ has been shown to have tumor-suppressive function in various cancers, including breast cancer. Recent studies have identified, synthesized, and tested the clinical safety of ERβ-selective agonists. The objective of this study was to investigate the utility of using ERβ agonists in the treatment of breast cancer.

To investigate the utility of ERβ agonists in the treatment of breast cancer, we used in-vitro and in-vivo pre-clinical models systems. Our results demonstrated that treatment with ERβ agonists, S-Equol and LY500307, was able to inhibit the short-term and long-term growth of both endocrine therapy sensitive and resistant breast cancer cells. Progression through the cell cycle, cell migration and cell invasion was also abrogated upon treatment. In-vivo, our syngeneic tumor mouse model demonstrates a decline in tumor growth rate after treating with a combination of letrozole and ERβ agonist. Gene expression array analysis reveal that treatment with ERβ agonist elicits changes in key signaling molecules involved in cell death and cell cycle pathways. In Letrozole resistant cells, Letrozole treatment had not effect on gene expression, while LY500307 treatment resulted in the modulation of 780 genes. Interestingly, combining Letrozole with LY500307 resulted in the modulation of 966 genes, of which 417 were unique to the combination treatment. Our studies suggest that activation of ERβ signaling is a valuable strategy in the treatment of breast cancer, even in cases which have developed resistance to current endocrine therapies.

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Cancer Research

Endocrinology

Abstract 3616: Potential therapeutic use of Estrogen Receptor β agonist in the prevention and progression of breast cancer using HER-2/neu mouse model

Kumaraguruparan Ramasamy, Cathy Samayoa, Naveen K. Krishnegowda, Ratna K. Vadlamudi, and Rajeshwar R. Tekmal
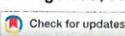
| Article | Info & Metrics |

Proceedings: AACR Annual Meeting 2017; April 1-5, 2017; Washington, DC

Abstract

Breast cancer is the most common cancer among women worldwide. Hormone-mediated therapy to treat estrogen receptor alpha (ERα) positive breast cancers include the use of ER antagonist, Tamoxifen, aromatase inhibitors and other compounds that degrade ERα. Unlike ERα, ERβ has been shown to have tumor-suppressive function in various cancers, including breast cancer. Recent studies have identified, synthesized, and tested the clinical safety of ERβ-selective agonists. Given the tumor-suppressive properties of ERβ, it may be possible to use these compounds to induce or activate the ERβ and test their role in the chemoprevention and blocking the progression of breast cancer. We have investigated the therapeutic utility of ERβ agonists in the prevention and progression of breast cancer using MMTV-HER2/neu mice transgenic mouse model. MMTV-HER2/neu mice develop premalignant lesions at 4-5 months, and tumors starting at month 7 due to overexpression of the HER2/neu proto-oncogene. MMTV-HER2/neu mice were treated with an ERβ agonist, LY500307 examined the prevention and progression of mammary cancers in these mice. When compared to controls, ERβ agonist-treated mice exhibited a significant decrease in the development of preneoplastic changes. Differential gene expression analysis revealed a significant change in the expression of a number of genes in response to LY500307 treatment. Pathway analysis identified an enrichment for chemokines signaling pathways, particularly TNF, in blocking the development of preneoplastic changes resulting from treatment with ERβ agonists. Our studies also show a decrease in the formation of mammary tumors in HER-2/neu mice with preexisting preneoplastic changes when treated with LY500307. This study suggests that ERβ agonist treatment may be a valuable therapeutic option for the prevention in women at increased risk of breast cancer and in blocking the progression of hormone receptor positive breast tumors.

Citation Format: Kumaraguruparan Ramasamy, Cathy Samayoa, Naveen K. Krishnegowda, Ratna K. Vadlamudi, Rajeshwar R. Tekmal. Potential therapeutic use of Estrogen Receptor β agonist in the prevention and progression of breast cancer using HER-2/neu mouse model [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2017; 2017 Apr 1-5; Washington, DC. Philadelphia (PA): AACR; Cancer Res 2017;77(13 Suppl):Abstract nr 3616. doi:10.1158/1538-7445.AM2017-3616

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